





## Advancements in 3D Bioprinting for Functional Tissue Engineering in Regenerative Medicine

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### ABSTRACT

3D bioprinting is a breakthrough fabrication technology in regenerative medicine. It offers great promise for fabricating hierarchical and heterogeneous tissues and organs with similar architecture as those of the natural ones. This review discusses recent advances in 3D bioprinting and the progress made for fabricating functional tissues, which have regenerative therapy applications. We cover the development of bioprinting methodologies, bioink composition and optimization, and incorporation of cellular and molecular signals for improving tissue function. An overview of the literature on key applications in skin, cartilage, bone and cardiovascular tissues is provided, including both preclinical achievements and clinical barriers/goals. In addition, we also talk about the contribution of bioprinted tissues for drug screening, disease modelling and personalized medicine. Regulatory and ethical aspects associated with the clinical translation of bioprinted tissues are also highlighted in this review. We present an up-to-date analysis of the recent literature (including studies from Nature, The Lancet, and BMC) as well as a data-rich viewpoint on 3D bioprinting to date in regenerative medicine.

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### INTRODUCTION

Regenerative medicine has seen remarkable progress due to the introduction of 3D bioprinting. Conventional tissue engineering strategies usually involve the use of static scaffolds and two-dimensional cell culturing systems, which do not reflect the complex composition and function compared with native tissues (1, 2). 3D bioprinting combats these challenges by providing the ability to deposit living cells and biomaterials on a layer-by-layer basis, thereby being able to produce tissue constructs with defined spatial orientation and cellular complexity (3).

Three-dimensional 3D bioprinting offers a paradigm shift in tissue engineering, enabling cells and biomaterials to be engineered together to create intricate tissue architectures. By finely patterning the

materials during their deposition (4), it is feasible to generate tissues that parallel the architecture and function of native organs. This ability carries important implications for regenerative medicine, and may provide potential answers in organ transplantation, disease modeling and drug screening (5).

The progress of 3D bioprinting technologies has been accelerated by the development in several aspects. It is essential to develop bioinks, which are biocompatible and can sustain the viability and functioning of the cells (6). These bioinks not only need to be able to support structure, but also encourage cell growth and differentiation. Furthermore, the development of printing techniques also improved the resolution and complexity of printed structures, as tissue with more complicated architecture could be created (7).



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One of the most exciting possibilities for 3D bioprinting is for regenerative medicine. Bioprinted skin replacements, for example, have been produced to help victims of burns as a substitute for conventional skin grafts. Also, bioprinted bone and cartilage tissues are being investigated as therapeutic approaches for musculoskeletal diseases. These applications also illustrate the multiple uses of 3D bioprinting technology for producing functional tissues that may be used to repair or replace damaged organs (8).

Although some problems persist even in the face of these accomplishments. Functional vascularization is a big challenge to achieve in bioprinted tissues due to the limited diffusion of nutrients and oxygen in large constructs. Additionally, more studies need to focus on the long-term stability and integration of BIOP tissues in the human body (9).

In summary, 3D bioprinting is a huge step for the area of regenerative medicine. Despite remaining obstacles, translating into the development of robust studies and advanced technologies has helped to improve this field significantly. With these challenges overcome, the vision of 3D bioprinting leading a paradigm shift in treating a number of different conditions comes closer to reality (10).

### Technological Evolution and Techniques

The technical development of 3D bio-printing has been characterized by iterative improvements in printing modalities, bioink compositions, and hardware systems, which together have allowed for the creation of progressively more intricate tissue constructs. Inkjet-based and extrusion-based systems have been widely used for early bioprinting techniques due to their disparate pros and cons (11). Inkjet bioprinting, based on the concept of conventional office inkjet printers, involves a controlled jetting process to eject picoliter droplets of cell-laden bioinks onto a surface. Thereby, deposition with high resolution within a couple of tens of micrometres (20–50  $\mu\text{m}$ ) can be achieved typically, which is particularly suitable to replicate fine tissue microarchitectures, like for capillary networks or neuronal layers (12). However, this method is restricted by the low viscosity range ( $\sim 10 \text{ mPa}\cdot\text{s}$ ) of bioinks that it can accommodate and may not allow incorporation of higher-cell-density suspensions or mechanically stiff hydrogels that more closely mimic the extracellular matrix (13).

In extrusion-based bioprinting, bioinks are deposited via continuous printing of filaments through a nozzle (2–300  $\mu\text{m}$ ), and it is capable of handling a wide range of liquid viscosities ( $306 \times 10^7 \text{ mPa}\cdot\text{s}$ ) (14). This makes it possible to, for example, print viscous hydrogels and composite bio-materials and even cell-laden polymer matrices that supply structural integrity to larger tissue constructs. Extrusion-based bioprinting

allows the generation of larger tissue volumes and mechanically supporting scaffolds, but it generally has lower spatial resolution (100–200  $\mu\text{m}$ ), which could compromise microarchitecture precision (15). Furthermore, shear stress in extrusion may influence cell viability, and so nozzle size, extrusion pressure and bioink rheology must be optimized to preserve functional cellular phenotypes (16).

More recently, hybrid bioprinting systems have been developed, which combine several printing modalities within the same system. Examples include systems which combine extrusion and inkjet processes that enable simultaneous deposition of mechanically-stable scaffold structures and high resolution cell patterns leading to improvement in both architectural fidelity and biological performance (17). Nozzle-free or laser-assisted bioprinting (LAB) is another technique that uses laser-induced forward transfer to deposit cell-laden droplets with high resolution (10–50  $\mu\text{m}$ ), so as to avoid using nozzles and reduce mechanical stress. LAB is highly suitable for printing high-viscosity bioinks (ICHS, 40 – 60  $\text{mPa}\cdot\text{s}$  and ECMs,  $\sim 10 \text{ Beta mPa}$ ) and sensitive cell types with low resistance to shear stress, such as neurons or myoblasts, yet scalability remains a hurdle (18).

Further developments are multi-material printing abilities, microfluidics-assisted bioprinting for graded pattern generation and real-time monitoring systems to confirm sharp layer superimposition and cell positions (19). Taken together, these technological advances are allowing the production of more sophisticated tissue constructs (e.g., vascularized bone, layered skin equivalents and organoids) and bringing 3D bioprinting closer to clinical translation in regenerative medicine. Iterative improvements to the instrumentation will further converge high-resolution, high-throughput, and multi-material strategies because of its small field-of-view (FOV and slow tip displacement (20).

### Bioinks: Composition and Optimization

Bioink preparation and optimization are a cornerstone in 3D bioprinting due to its dual role as a structural support and regulator of the local biology. An ideal bioink should meet several key requirements: high biocompatibility for the survival and proliferation of cells, proper mechanical properties to retain its shape during and after printing, adjustability in degradation rate at a similar pace as cell maturation, and bioactivity promoting vascularization that influences cell differentiation and tissue growth (21). Optimization of these parameters can be difficult as they are typically interdependent: e.g., increasing the polymer concentration could improve mechanical stability at the same time that it increases viscosity, which could compromise printability and reduce cell viability (22). Owing to their biocompatibility and the resemblance of

their structure to native extracellular matrices (ECM), natural polymers have been extensively used. One such biomaterial is alginate, extracted from brown algae, that has been utilized for its mild gelation through ionic crosslinking with divalent cations like  $\text{Ca}^{2+}$ , which allows encapsulation of delicate cell types (23). Unfortunately, alginate does not contain cell-adhesive motifs and must therefore be modified with RGD peptides or combined with other ECM proteins. Gelatin is a denatured collagen with good cell spreading characteristics and bioresorbability, which can be modified to form gelatin methacrylate (GelMA) for UV-crosslinking purposes that provide spatial control during printing (24). Collagen per se, the most frequent ECM protein in mammals, presents intrinsic signaling cues for cell attachment, proliferation and lineage-committed differentiation; however, its mechanical stability is typically insufficient to be used alone and must be reinforced with synthetic polymers or crosslinkers. Hyaluronic acid and fibrin are also commonly used materials to mimic tissue-specific ECM environments, especially in the case of cartilage and vascular tissues, where they promote cell migration and angiogenesis (25).

Tunability of synthetic polymers such as PEG (polyethylene glycol), PLA (polylactic acid), PGA (polyglycolic acid) and PCL 106 (polycaprolactone), in mechanical properties, degradation rates, and chemical functionalization is offered. For example, PEG-based hydrogels have been designed with tunable Young's modulus from 0.5 to 50 kPa to mimic soft tissue or cartilage microenvironment, and PCL provides superior mechanical support for load-bearing structures, e.g., bone tissue scaffolds. Combining synthetic and natural polymers allows to combination of the biological cues of natural matrices, with the strong mechanical features of synthetics: this offers new possibilities in bioink formulations for various tissue types (26).

Besides the structural composition, the introduction of bioactive molecules is also important for the interaction with cells and the maturation of tissues. Growth factors (for example, VEGF, BMP-2 and FGF-2) may be incorporated into bioinks or attached to polymer backbones for sustained localized signaling for stimulating angiogenesis, osteogenesis or fibroblast proliferation (27). Short peptides, like RGD, IKVAV and YIGSR that are analogues of specific ECM binding domains, are used to promote integrin-mediated adhesion and cytoskeletal assembly. In addition, extracellular vesicles, cytokines or small bioactive molecules can be supplemented to modulate the cellular metabolism, differentiation paths and immunomodulatory responses to further enhance the functionality of tissue (28).

Tuning rheological properties to enable fast extrusion

and cell protection through shear-thinning behavior, and a rapid recovery of viscosity for printed shape preservation is often sought. Ionic, thermal, enzymatic and photo-crosslinking are the crosslink types applied depending on the requirements for the mechanical strength, degradation or biocompatibility (29). Technologically more advanced methods also make use of gradient bioinks where mechanical and biological factors change in space within a construct, to mimic tissue inhomogeneity as well as to improve the maturation of complex structures like osteochondral interfaces or vascularized tissue (30).

### Cellular and Molecular Integration

For effective tissue engineering, cellular and molecular elements must be assembled into the organized systems found in native tissues. Enrichment with the right cell types is not enough: the microenvironment, with associated biochemical signals, mechanical influences and spatial organization; also strongly instructs to determine cell behaviour, differentiation and tissue maturation (31). There is a need to carefully select the cell components as per the tissue. For example, vasculature tissue requires the presence of endothelial cells to establish a perfusable network and the fibroblasts are needed for the synthesis and remodeling of the extracellular matrix (ECM). Osteoblasts, osteoclasts and mesenchymal stem cells in bone tissue must work together dynamically for the mineralization and architecture of bones to be correct (32).

Exact proportions of hepatocytes, Kupffer cells and hepatic stellate cells are also necessary in liver constructs to mimic metabolic and detoxification functions. The organization of cells in bioprinted constructs is also an important factor for tissue function (33). Native tissues have a hierarchical structure and heterogeneous cell types distribution, such as in the skin where keratinocytes build up the epidermal layer, melanocytes scattered among with for coloring cutaneous layers, while below is the dermis housing fibroblasts living in ECM equilibrium (34). It is critical to reproduce this organization in vitro to obtain a morphology and function which are physiologically relevant. Sophisticated 3D bioprinting techniques involving extrusion-based, inkjet, and laser-assisted methods facilitate accurate multi-cell deposition in predetermined patterns with spatial heterogeneity that closely resembles that of the in vivo tissue (35). The multi-nozzle printing and microfluidic-assisted systems allow for even greater control of the ability to gradient cell density, ECM composition, and growth factors, which are critical in directing tissue development.

At the molecular level, cells and their microenvironments are composed of extracellular matrix (ECM) components, soluble signaling factors, and mechanical

signals (36). ECM proteins like collagen, laminin, and fibronectin have been proven to offer not only structural support but also biochemical signals to direct cell adhesion, migration and differentiation. Soluble factors such as growth factors (e.g., VEGF, BMPs, FGFs) play a pivotal role in both lineage-specific differentiation induction and angiogenesis in the tissue constructs (37). Mechanical stimuli, e.g. substrate stiffness and shear stress, regulate the cytoskeletal organisation, mechanotransduction signalling pathways and gene expression, which dictate cell fate decisions. Advanced bioprinting permits the introduction of these molecular signals in regions defined by location, generating microenvironments that closely mimic native tissue niches (38).

Vascularization remains a significant challenge for the engineering of functional tissues, as diffusion is inadequate to maintain cell viability in constructs over 200–500  $\mu\text{m}$ . While approaches to incorporate endothelial cells, pericytes and angiogenic factors within bioprinted constructs have proven effective at creating perfusable vascular networks (39). Endothelial cells and supporting stromal cells co-cultured in defined spatial geometry can self-assemble into lumenized capillary-like structures, which can be modified using VEGF gradients to promote vessel sprouting and maturity. Such strategies are essential for the long-term survival and function of tissues, especially thicker or metabolically active constructs such as heart muscle or liver organoids (40).

The incorporation of immune cells, or factors to modulate the immune response in bioprinted constructs, can further replicate a more physiologically appropriate microenvironment for enhanced tissue homeostasis and tunable integration following implantation (41). For instance, macrophages in 3D tissues can affect ECM turnover and angiogenesis, or T-cell interactions could be crucial for particular immunocompetent tissue models (42). Moreover, with the help of advanced 3D bioprinting platforms, it also becomes possible to tailor temporal and spatial stimuli dynamically, for example, through temporarily controlled deposition of growth factors or staged maturation of cell populations in a printed construct so that the resulting tissue more closely follows developmental processes leading to better functional performance (43).

### Applications in Regenerative Medicine

The uses of 3D bioprinted tissues for regenerative medicine are wide-ranging/in the breadth of clinical applications, from wound healing, musculoskeletal repair, to organ construct and disease modeling/disease models or physiologically relevant in vitro drug/platforms. In dermatology, the production of bioprinted skin substitutes is an area of particular interest because there is a clinical need for effective

therapies against burns, chronic ulcers or other severe traumatic injuries to the skin (44). For such constructs, keratinocytes are generally added to make an epidermal layer, and fibroblasts are dispersed in a dermal like extracellular matrix, occasionally with additional melanocytes or endothelial cells to enhance pigmentation and vascularisation. Research studies have already shown that bioprinted skin substitutes can increase wound healing, angiogenesis and barrier function restoration more efficiently compared to conventional grafts, leading to a 30–40% rise in re-epithelialization rates – all from preclinical testing (45). In addition, skin equivalents with well-defined dermal epidermal junctions that are beneficial for (i) enhanced structural fidelity and iii) function have also been achieved using stratifying bioprinting approaches (46).

For the field of cartilage repair, 3D printing offers the potential to generate constructs that mimic the anisotropic and viscoelastic response of native cartilage. By employing hydrogels loaded with chondrocytes or mesenchymal stem cells (MSCs), the compressive moduli of bioprinted cartilage constructs could reach 0.2 to 2 MPa, which is similar to native articular cartilage (47). These constructs dictate cell and ECM component deposition across space, which thereby influence cellular differentiation, matrix production and ingrowth with the host tissue. Moreover, gradient-based bioprinting methods enable the generation of osteochondral tissue with a gradient from cartilage to sub-chondral bone, which contributes to the long-term function for joint repair purposes. Preclinical proof in rabbits and pigs revealed significantly-enhanced defect filling, less inflammation, as well as joint mechanics rescue and accordingly full clinical translation potential (48).

3D bioprinting has also proven advantageous in the field of bone tissue engineering, especially for patient-specific scaffolds corresponding to defect geometries from CT or MRI images. Osteoprogenitor cells are mixed with hydroxyapatite, tricalcium phosphate or polycaprolactone to generate scaffolds that stimulate osteogenesis and vascularity (49). The addition of anabolic molecules, such as BMP-2 or VEGF, locally improves bone mineralization and vascular growth, with up to forty to sixty percent more bone volume fraction found in vivo within the implanted scaffolds compared to non-bioactive controls. These techniques allow more predictable outcomes for craniofacial, orthopedic and dental reconstructions and decrease dependence on autologous bone grafts with the associated donor site morbidity (50).

Vascularization represents an important challenge for the clinical translation of bioprinted tissues because cell survival is limited within fabricated constructs larger than 200–500  $\mu\text{m}$  due to diffusion (51). This

challenge is beginning to be overcome with advances in 3D bioprinting that have introduced perfusable vascular networks and microfluidic-supported designs. Simultaneous co-printing of endothelial cells and supportive stromal cells in the presence of angiogenic growth factors enables the construction of interconnected capillary-like structures, while sacrificial bioinks are used for forming hollow channels, which, after being endothelialized into vessels, become functional (52). In preclinical settings, the vascularized bioprinted tissues show increased oxygen and nutrient supply along with decreased necrosis and better integration with the host vasculature following implantation. For instance, for bioprinted heart patches, it has been demonstrated that pre-formed microvasculature enhances cardiomyocyte survival, raises contractile function, and increases engraftment rates, demonstrating the therapeutic potential of vascularized constructs for regenerative application to metabolically demanding tissue (53).

### Preclinical and Clinical Insights

A wealth of preclinical studies have presented convincing data, validating the feasibility and therapeutic effects of 3D bioprinted tissue in various tissues. Nothing in dermatology Their Review discusses the wide utilization of bioprinted skin constructs. Pioneers bioprinted skins concepts have been thoroughly examined on murine, porcine, and rabbit models (54). These reports indicate that tissue equivalents containing keratinocytes and fibroblasts, often in combination with endothelial cells, improve wound contraction but also enhance functional tissue integration. Histological analysis demonstrates organized epidermal layers and development of dermal papillae and deposition of native-like extracellular matrix, with increased vascularity in constructs containing pre-vascularized networks (55). Over quantitative scales, wound closure rates in treated animal models frequently increase by 30–50% over conventional grafts and superior tensile strength and barrier function suggest better tissue maturation. These findings highlight the translational potential of bioprinted dermal substitutes for burns, chronic ulcers, and other difficult wounds (56).

Bioprinted bone constructs have also performed successfully in preclinical models. Using osteogenic cells seeded onto composites of hydroxyapatite, tricalcium phosphate, or biodegradable polymer scaffold, such constructs have demonstrated substantial osteointegration and new bone formation in small- and large-animal models (57). Using micro-computed tomography (micro-CT) studies often describe a 40–60% rise of bone volume fraction within implanted scaffolds over 8–12 weeks, with evidence of vascular infiltration and mineralization morphologically similar to native bone architecture (58). For craniofacial and

orthopedic defect applications, anatomically relevant geometries from imaging data increase scaffold fit and mechanical stability to promote functional repair and limit further surgical procedures. Similarly, preclinical studies have demonstrated that the addition of angiogenic factors including VEGF facilitates neovascularization, an important aspect of long-term tissue survival and remodeling (59).

Notwithstanding this optimism, the translation of bioprinted tissue constructs from preclinical models toward human clinics faces multiple significant challenges. The first is the technical challenge of scaling up production simultaneously with maintaining cell viability, uniformity, and structural fidelity (60). The volumes of constructs intended for human implantation are frequently many orders of magnitude higher than required for animal studies, and require tuning bioprinting speed, nozzle geometry, and bioink viscoelastic properties to ensure that the cells maintain viability during deposition (61). Second, it is important to maintain the long-term function of implanted tissues. Although short-term results including initial engraftment, vascularization, structural integrity can be obtained in preclinical models, longitudinal studies will be required for demonstrating maintenance of tissue function, integration with host tissues and lack of detrimental immune or fibrotic encapsulation. For instance, in the field of bone tissue engineering, preservation of load-bearing capacity and prevention of resorption over long time periods is still a priority (62).

Regulatory requirements further complicate clinical translation. Regulatory agencies, including the FDA and EMA, mandate rigorous preclinical testing, including biocompatibility, toxicity, tumorigenicity, and immunogenicity assessments, before permitting clinical trials (63). Inflammation is a key driver of cancer initiation, metastasis and resistance to therapy. The ability to regulate inflammation by itself, and in synergy with conventional and newer anticancer agents has significant potential to increase the sensitivity of treatment and eventually improve patient outcomes. Having developed an improved understanding of the complex interplay between inflammation and the tumour microenvironment, there is now a clear imperative to develop personalised and disease-context specific anti-inflammatory therapies. In the years to come, we need to focus on finding new ways for patient stratification, novel and safe anti-inflammatory drugs and their integration in clinical practice. PAVE'ing the way and advancing these efforts into well-designed clinical trials will be important for translating new preclinical data to rational, effective therapies that can benefit more patients with cancer (64).

Early-phase clinical trials have begun exploring bioprinted tissue applications. For example, pilot

studies of bioprinted skin grafts in patients with burn injuries have reported favorable engraftment rates and minimal adverse events, although sample sizes remain limited and follow-up durations are short. Similarly, bioprinted cartilage and bone scaffolds have been implanted in small cohorts for reconstructive surgeries, demonstrating feasibility but highlighting challenges in achieving full functional restoration and integration (65).

### Regulatory and Ethical Considerations

For the translation of 3D bioprinted organs into clinical use, it will be necessary to have a full and robust regulatory process that assures safety, reproducibility and efficacy for the patient. Regulatory bodies, including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (2), and other national health authorities mandate stringent preclinical and clinical evaluation of bioprinted constructs prior to their approval for human use (66). From pre-clinical data it should be clear, that the carrier is biocompatible (bio-compatibility investigation), non-toxic and nonimmunogenetic, long-standing implanted in a living system without any damage or loss of its structural stability, functional integration and/or induction of an undesired tissue response like fibrosis or tumorigenicity. For constructs integrated with multiple cell types or bioactive factors, additional characterization of cellular responses, gene signatures and biomolecular interactions is needed to guarantee the predictability of biological outcomes (67). Standardization of bioink formulation, printing conditions and post-processing procedures are necessary to guarantee reproducibility from batch to batch which is essential for regulatory approval (68).

Regulatory and ethical control is also required in the area of post-market monitoring following approval for clinical use of bioprinted tissues. Continuous surveillance for long-term results, complications and biological integration is required to maintain safety and effectiveness (69). Data obtained from these surveillance programs can be used to facilitate an iterative cycle of refinement in bioink compositions, printing modalities and clinical practice that will improve regulatory compliance and patient benefit (70).

### Future Perspectives

The transformative nature of the 3D bioprinting process in regenerative medicine will revolutionize tissue engineering, due to rapid strides made in biomaterials, 3D printing techniques and cell biology. The ultimate goal is to develop 3D, in vitro vascularized and innervated tissues suitable for organ replacement or repair (71). This is currently an active area of research, as investigators are exploring a number of advanced “smart” bioinks such as stimuli-responsive

hydrogels and composite formulations that include natural ECM components and synthetic polymers those can respond dynamically to host physiology and regulate stiffness and degradation, provide biochemical cues for promoting integration and long-term activity. These bioinks have been developed to mimic the tissue-specific mechanical heterogeneity, consistent with that of osteochondral or myocardial interfaces (72). Collectively, these approaches will drive the development of personalized regenerative strategies encapsulating patient-derived cells, OOC platforms and rich disease models to impact applications in tissue replacement, drug discovery and disease modeling by closing the gap between the bench and bedside (73).

### CONCLUSION

3D bioprinting is a transformative technology in regenerative medicine that enables the fabrication of functional patterned tissue with well-defined microarchitecture and biomimetic microenvironment. Preclinical models have shown the greatest potential for skin, cartilage and bone repair but improvements in vascularization, bioink development and multi-cellular integration are slowly overcoming some of its limitations. The ultimate clinical promise of 3D bioprinting will be actualized by continued interdisciplinary synergy between materials science, cellular biology, engineering and clinical medicine and rigorous regulatory mandate for ethical considerations. With these converging efforts, 3D bioprinting is emerging as a potential pillar of personalized regenerative medicine solutions to support tissue transplantation and organ repairs while also enabling drug testing against patient-specific disease models.

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Farnaz Roshan Mehr and Fatemeh Gabeleh data curation; editing and review. The authors read and confirmed the final manuscript.

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### Conflict of Interest

The authors declared no conflict of interest.

### Consent for publication

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